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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,139	THIEDE ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/30/2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a 371 national stage filing of PCT/US99/26927, filed November 12, 1999, which claims benefit to provisional application 60/108,357, filed November 13, 1998.

Applicants' amendment filed January 30, 2006 has been received and entered. Claims 1-5, 9-27 have been canceled. Claims 6-8 are pending.

For clarity, it is noted that the term "isolated" has been added to claim 6, and that in utero (underlined in claim) was present in the original claims.

Election/Restriction

Applicant's election of group II, claims 6-8, with traverse was acknowledged. It was noted that because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Claims 1-5, 9-27 drawn to nonelected inventions have been canceled, and no new arguments have been provided.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

The disclosure is objected to because of the following informalities:

the nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825.

37 CFR 1.821(d) states: "[w]here the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description of claims, even if the sequence is also embedded in the text or the description or claims of the patent application.

In this case, upon review of the specification, sequences on page 18 have been identified which do not have SEQ ID NOs. Further, there has not been a sequence listing provided for the instant application.

Appropriate correction is required.

The absence of proper sequence listing did not preclude the examination on the merits however, **for a complete response to this office action, applicant must submit the required material for sequence compliance.**

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 6-8 stand rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a well asserted utility or a well established utility.

Applicants argue that once it has been established that mesenchymal stem cells have distributed throughout an animal after administration to a fetus *in utero*, the skilled artisan would

expect reasonably that such mesenchymal stem cells could replace defective cells as they become damaged (page 4, 2nd paragraph). This is not found persuasive because damage or degenerative diseases do not result uniquely from deficiencies of the cell itself, and thus providing a cell in advance would not provide a source of cells for regeneration. The specification does not provide any specific example of the above, so by way of example degenerative diseases or tissue damage caused in liver cirrhosis or radiation therapy would not clearly not benefit from having a secondary source of cells. In these two cases the damage and affect is on the cells of the subject regardless of their source. Similarly, any damage not directly related to the cell itself will not benefit from having a source of other cells present. Moreover, even degeneration/damage caused by a particular cell can have an affect on surrounding cells. For example, one cause of diabetes is the loss of insulin producing cells when the individual produces antibodies to its own cells that produce insulin. In this case, the presence of a reserve of cells would fail to provide any benefit to a subject. Applicants argument and assertion that the skilled artisan would "expect reasonably that such mesenchymal stem cells...replace defective cells as they become damaged" (page 4) is not supported by any evidence to this expectation, in particular as it broadly encompass any tissue damage or degeneration. Moreover, the specification does not provide any support for this expectation and given the examples above, there does not appear to be reasonable scientific support of this expectation of the skilled artisan. For the sake of completeness, it is noted that the arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence

that is required to rebut a prima facie case of obviousness."). See MPEP § 716.01(c) for examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration.

Similarly, for muscular dystrophy, osteoporosis, osteogenesis imperfecta or collagen disorders where there can be an identifiable genetic alteration affecting the cell itself, Applicants assert that the present invention will provide normal cells that will differentiate into normal cells, and the skilled artisan would readily appreciate that the normal cells will provide a benefit to counteract the affect of the cells specifically associated with the disorder (pages 4-5). This is not found persuasive because the assertion is not supported by the process in which collagen is assembled. In this case, it is presumed that cells are not replaced but are present and simply supply a source of collagen that is not altered (as would be consistent with any one of the diseases). Collagen molecules are synthesized, and pro-collagen is processed before assembly into the fibrils that make-up the intracellular matrix. Given the inherent properties of the process of collagen synthesis, given the presence of cells that produce both normal and altered forms of collagen, the skilled artisan would reasonably expect that altered and normal forms of collagen would be secreted and present in the extracellular matrix. It is noted also, that osteogenesis imperfecta affects individuals that are heterozygous and homozygous for the α-1 chain allele. Clearly, with respect to this disorder, even having present a normal copy of gene fails to remedy the disorder. Osteogenesis imperfecta does not result in cell loss or degeneration only in the production of an altered extracellular matrix as a consequence of expression of a mutant collagen protein and all the problems associated with this. By extension, providing an additional cell source that has a normal copy and produces a α-1 chain would fail to ameliorate the problem of

the mutant form produced and incorporated into the collagen matrix. With respect to MS, the mechanisms of this disorder is similar to that discussed with diabetes, in that it is a form of auto-immune disease where the subject makes antibodies and destroys the myelin sheath encircling the nerve cells in a subject. As discussed above, it would not matter what the source of cells is when the affect is a consequence outside the cell.

Examiner does not contest that the art of record and the specification teaches and provides evidence that hemopoetic cells and in particular mesenchymal stem cells can be transplanted *in utero* and that the implanted cells will distribute throughout the fetus, in some cases differentiating into cell types of organ in which they implanted. However, based on the teachings of the specification proposing only potential clinical applications of: "1) large scale tissue engineering particularly for repair of musculoskeletal injury; 2) cellular therapy for diseases of mesenchymal origin such as muscular dystrophy, osteoporosis, osteogenesis imperfecta, and collagen disorders; 3) bone marrow conditioning to facilitate engraftment of autologous or allogeneic hematopoietic stem cells; and 4) gene therapy." (page 25), and that "[P]renatal MSC transplantation may provide a "reservoir" of normal stem cells to replace defective cells as they become damaged in degenerative diseases with progressive cellular and organ damage." (page 25), it is maintained that in light of the basis of the rejection which focuses on the fact that while the specification reduces to practice the *in utero* transplantation of mesenchymal stem cells, and that the cells appear to distribute throughout the organs in the engrafted animal, the specification fails to provide a nexus wherein this phenomena will result in any of the proposed utilities.

Applicants appear to rely on the utility provided and discussed above, and do not provide arguments for the other asserted utilities disclosed and discussed in the basis of the rejection. For the sake of completeness it is noted that with respect to tissue engineering the specification fails to provide any specific guidance on how a chimeric organ would or could be used in any context. Further, while it is acknowledged that mesenchymal cells implanted *in utero* will distribute into various tissues and organs in the fetus and be detectable in the resulting animal, the process by which this occurs is random and not subject any specific manipulation which would be consistent with generating a engineered tissue for further use. Moreover, with respect to using the engineered tissue for repair of musculoskeletal injury or in treating diseases of mesenchymal origin, there is no objective evidence that the implanted cells will obviate any specific damage that is present or will counter act any potential damage in diseases such as muscular dystrophy, osteoporosis, osteogenesis imperfecta or collagen disorders. For example, if an altered form of collagen is expressed by the cells of the host animal, it is unclear how providing a second source of collagen would alleviate any of the consequences of the altered collagen. The altered form of collagen would be present and the consequences of its presence would still be maintained resulting in the same condition associated with a given disorder. With respect to conditioning a tissue for engraftment, it may be that any resulting tissue from an animal implanted with mesenchymal stem cells could possess antigens of the animal into which it would be transplanted, however this affect would not counter all the foreign antigens associated with the donor. Thus, while the tissue may contain cells that would not be recognized as foreign relative to the animal in which it is to be delivered, the potential for rejection is not counteracted relative to the foreign antigens that still exist within that tissue. Finally, with

respect to the use of the method for gene therapy, it is unclear how the present method would be used to affect gene therapy. Currently, the art recognizes multiple limitations to affecting gene therapy including problems with gene delivery and gene expression, and it is unclear how the present method would be sued specifically to ameliorate any of the art recognized problems. Moreover, even in methods which appear to be affective in treating certain symptoms of a given disease, there is no guidance on how these gene therapy methods should be adapted with the methods as claimed.

Again, it should be noted that the basis of the rejection does not focus on the clinical applicability of the claimed method, rather the fundamental applications as proposed. As reasoned above, each of the proposed utilities do not represent methodology common in the art and lack any specific real world context for use. It may be argued that the claimed method meets the utility requirement in that "an invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications" (*Carl Zeus Stiftung v. Renishaw PLC*, 945 F.2d 1173, 20 USPQ2d 1094 (Fed. Cir. 1991)). However, in the instant case, the claims lack utility not because they are incomplete, and not because they do not set forth the best or only way to accomplish a result, and not because they are not unique, but because they do not have either a well-established utility or a specific and substantial asserted utility. Applicants arguments in all responses have focused on only one of the cited utilities that is MSC transplantation may provide a "reservoir" of normal stem cells to replace defective cells as they become damaged in degenerative diseases with progressive cellular and organ damage (page 25), and have not provided any discussion for the use in (1) large scale tissue engineering particularly for repair of musculoskeletal injury; 2) cellular therapy for diseases of mesenchymal

origin such as muscular dystrophy, osteoporosis, osteogenesis imperfecta, and collagen disorders; 3) bone marrow conditioning to facilitate engraftment of autologous or allogeneic hematopoietic stem cells; and 4) gene therapy; each of which are in part representative of the ability of the implanted cells to act in a tissue or organ to affect the desired treatment (previous office action page 3 and page 25 of the specification). While the Examiner has acknowledged the working examples in the specification but indicated that the basis of the rejection focuses on the fact that while the specification reduces to practice the *in utero* transplantation of mesenchymal stem cells, the specification fails to provide a nexus wherein the observed phenomena and the proposed utilities (bottom of page 3 of the previous office action). Further, it was noted that the basis of the rejection focuses on the fundamental applications as proposed by the specification, and not the potential clinical problems or applicability. Finally, it was acknowledged by the Examiner in part that a claimed invention need not teach the best method of accomplishing a particular task, and only need be useful to some extent or in accomplishing certain applications, citing *Carl Zeus Stiftung v. Renishaw*. However, contrary to Applicants' assertion the ability of a cell to implant and differentiate does not make it a reservoir of cells in cases of a degenerative disease. First, the specification does not teach what degenerative diseases can be affect by *in utero* implantation. Moreover, it does not provide a basis for why the implanted cell would be immune to the affects of any given degenerative disorder. For example, there are several degenerative disorders associated with the immune system wherein the immune system attacks antigens present on a cell such as in diabetes or MS, and it is unclear how an implanted cell will avoid the immune system in these diseases. In another example, the presence of an implanted cell does not make immune to external insults that result in a

degenerative disorder such cirrhosis of the liver or affects of toxic or carcinogenic compounds. As noted in Applicants arguments the specification asserts a utility that has been thoroughly considered but demonstrated to neither substantial nor specific even in light of the working examples. Again, it is not contended that implantation of cells will not occur, rather it is maintained that practicing this method has not specific nor substantial utility because these cells do not act as reservoirs in degenerative disease cases as asserted by the specification.

Claim Rejections - 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-8 stand also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a well asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants summarize the basis of the rejection noting the citation of Mackenzie *et al.*, and argue that even if further investigation is required, that would not mean that the skilled artisan would not reasonably expect that transplanted mesenchymal stem cells would treat various diseases (page 5-6). Discussing the results of Mackenzie *et al.* Applicants argue that similar to their results, one skilled in the art would expect that mesenchymal stem cells would differentiate into various cell types in sufficient amounts to counteract various diseases and disorders (page 6). Applciants arguments have been fully considered, but not found persuasive.

As discussed above, the point of the rejection is not that mesenchymal cells will not implant themselves when administered *in utero*, rather that the specification fails to teach any specific or substantial circumstance to practice the method as claimed to provide a reservoir of stem cells or any of the other proposed utilities, in a fetus or resulting animal. Examiner does not contest the ability of mesenchymal stem cells to differentiate into various cell types when transplanted into a fetus *in utero*, rather the specification provides insufficient guidance and teaching on how to accomplish the proposed utilities specifically set forth. More clearly stated, Examiner would agree that one could follow the single method step required by the instant claims, however, the basis of this rejection is to why the skilled artisan would practice this method. Based on the guidance provided by the instant specification, a detailed discussion of why Applicants proposed uses fail to provide adequate guidance for any form of treatment or practicing the method of engraftment as broadly set forth in the instant claims. Mackenzie *et al.* was provided as point for analogy that the method step could be successfully practiced, however that even today there are does not appear to be therapeutic applications. Mackenzie *et al.* and Santner-Nanan *et al.* were provided to support the assessment of the Examiner of Applicants specification and the proposed uses as would be viewed by the skilled artisan at the time of filing and today.

Examiner has provided sound scientific reasoning to why each of the specific proposed uses for practicing the claimed method would not work, and in view of the high degree of unpredictability associated with the proposed utilities of the claimed method recognized by the skilled artisan even today, underscores the need to provide teachings in the specification that would provide the artisan with specific guidance or regimens for use of an engineered tissue that

would result form the method or that achieve for example a therapeutic benefit in gene therapy methods. However, the specification does not provide such guidance, and the general guidance provided and appears to be based on a scientifically flawed premise.

Without the necessary guidance in the specification and the lack of correlative working examples for practical applications, the claims would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan. Thus, in view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would require undue experimentation by one of skill to practice the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 6-8 stand rejected under 35 U.S.C. 102(b) as being anticipated by Diukman *et al.* (J Reprod Med June 1992 37(6):515-520).

Claims 6-8 stand rejected under 35 U.S.C. 102(b) as being anticipated by Barnes *et al.* (J Med Genet Feb 1983 20(1) 41-45).

Claim 6 has been amended to recited the administration of "isolated msenchymal stem cells". It is noted that "isolated" is not specifically defined in the specification, and support for the use in the claimed methods finds the figurative support from the general disclosure of obtaining mesenchymal stem cells. In assessing the breadth of what is encompassed by the claims, a review of the specification describes and provides a specific example (working example 1 –page 13) where mesenchymal stem cells were isolated using a density gradient and the resulting population of isolated cells was described as enriched (line 25). Clearly, as provided in this example and generally by other methods known in the art (and relied upon by the specification-page 13, lines 16-19 for example) various "isolation" methods result in different compositions comprising isolated mesenchymal stem cells. In this case, given the guidance of the present specification, the broadest reasonable interpretation of isolated mesenchymal stem cells comprises the use of any isolated composition comprising mesenchymal stem cells. Isolated is being considered to encompass simply removing a source of mesenchymal stem cells because the absolute nature or requirements encompassed by the composition that is isolated is not specifically set forth in the specification and examples clearly provide support that the population is simply enriched, not a purified population of a unique cell type. In light of the discussion above, claim 6 is still broad and encompasses methodology that simply requires the administration of compositions comprising isolated mesenchymal stem cells. As supported by the instant specification (page 2, lines 15-18), that mesenchymal stem cells reside in many sources including bone marrow and the blood. Claim 6 broadly reads on providing one of these sources wherein mesenchymal stem cells reside to a fetus *in utero*.

Applicants argue that nether Diukman *et al.* nor Barnes *et al.* provide for isolated mesenchymal stem cells. See Applicants' arguments, page 3. Applicants' arguments have been fully considered, but not found persuasive.

As discussed above, the amendment to the claims is noted, however given the guidance of the instant specification, the claims still broadly encompass the administration of isolated compositions that comprise mesenchymal stem cells. As stated previously, Diukman *et al.* teach animal models where mouse, sheep and rhesus monkey receive *in utero* stem cell transplantation of bone marrow. Further, Diukman *et al.* teach that in light of animal studies, this methodology is being practiced in humans and that human trials are underway. Barnes *et al.* teach animal models where human whole blood is injected intrauterine into rabbits and rhesus monkey. Each receive *in utero* stem cell transplantation present in the blood. Further, Barnes *et al.* teach that in light of animal studies, this methodology is under consideration for approaches to correct certain inherited diseases in humans. In each case, given the broadest reasonable interpretation of the claims, both Diukman *et al.*and Barnes *et al.* anticipate the claimed invention.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach